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Pulmonary Transplantation and Ischemia-Reperfusion Injury

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1. Introduction

Lung transplantation provides a curative hope for many with end-stage pulmonary disease. Since the first attempt at human lung transplantation in 1963, scientific and surgical advancements have supported improved survival and quality of life for lung transplant recipients (Hardy, et al., 1963). Significant contributions in cardiopulmonary bypass, pharmacologic immunosuppression, and donor-recipient risk stratification have increased the success and associated clinical adoption of this treatment strategy. Continued research efforts in novel methods for organ preservation, donor graft selection, and recipient risk stratification support a promising future for lung transplantation.

Improvements in surgical technique and perioperative care over the past two decades have led to a 30-fold increase in the number of lung transplant recipients worldwide to 2,769 patients in 2008 (Christie, et al., 2010). Since 1994, bilateral lung transplantation has supplanted single lung transplantation as the primary strategy for organ replacement to now account for 71% of lung transplants performed worldwide (Christie, et al., 2010). In 2010, the primary indications for lung transplantation included chronic obstructive pulmonary disease (35.5%), idiopathic pulmonary fibrosis (22.1%), and cystic fibrosis (16.0%) (Christie, et al., 2010). Despite this promising evolution and the increasing number of indications for lung transplantation, long-term survival has shown minimal improvement. Lung transplant outcomes remain the poorest of any solid organ transplant, with international survival estimates demonstrating a 21% one-year and 50% five-year mortality (Christie, et al., 2010).

Lung ischemia-reperfusion (IR) injury following transplantation imposes a significant threat to graft and recipient survival (Diamond & Christie, 2010). IR injury is the main cause of primary graft failure and significantly increases the risk for acute rejection and long-term graft dysfunction (de Perrot, et al., 2003). Multivariate analysis of long-term graft function has implicated IR injury as an independent predictor for bronchiolitis obliterans syndrome (BOS), the most common cause of long-term morbidity and mortality after lung transplantation (Fiser, et al., 2002). IR-induced lung injury is characterized by nonspecific alveolar damage, lung edema, and hypoxemia occurring within 72 hours after lung transplantation (de Perrot, et al., 2003). The estimated incidence of IR injury is 41% following lung transplantation with an associated 30-day mortality of 40%, compared to 7% for

patients with no IR injury (Granton, 2006). Clinical studies have demonstrated increased in-hospital mortality and morbidity associated with IR injury resulting in prolonged ventilation, postoperative systolic pulmonary hypertension, longer intensive care unit stay, and increased cost of hospitalization (Cottini, et al., 2006; King, et al., 2000).

Currently no clinical therapies are available to prevent IR injury. The standard method used to help minimize IR injury for lung transplantation incorporates a universal cold crystalloid flush of the donor organ prior to explantation. Cold storage on ice during the preservation period limits metabolic activity, vasospasm, and thrombosis (Puri & Patterson, 2008). Reimplantation into the recipient restores warm perfusion to the allograft, initiating a characteristic inflammatory cascade leading to IR injury. Hypothermic organ storage is associated with oxidative stress, sodium pump inactivation, intracellular calcium overload, iron release, and cell death that induce cell surface expression patterns and proinflammatory mediators for leukocyte activation during the reperfusion period (de Perrot, et al., 2003). This inherent response mechanism implicates IR injury as a primary determinant of both immediate and long-term graft survival.

Quality of the donor allograft and nature of recipient pathophysiology are primary determinants for the severity of IR injury, with a defined spectrum from mild pulmonary infiltration to the most severe acute respiratory distress syndrome (King, et al., 2000). A significant research commitment in lung transplantation is focused on organ selection and preservation to limit the deleterious effects of IR injury. Currently a disparaging 10-30% of donor lungs are approved for transplantation based on predictive criteria incorporating donor history, arterial blood gas assessment, chest x-ray and bronchoscopic findings, and physical examination upon lung retrieval. Inherent limitations are present in the subjective assessment of the donor allograft, as evidenced in comparable outcomes with extended donor criteria with marginal donor organs (Sundaresan, et al., 1995). This finding supports continued research commitment to risk stratification and predictive modeling for IR injury in donor lung selection.

Allograft selection and donor pool expansion are primary aims for current lung transplantation research. Traditional organ procurements for lung transplantation involve donation following brain death, excluding donations after cardiac death as a result of the inherent extended period of ischemia. Study of systemic markers for inflammation in brain dead donors has established interleukin-8 as a predictive cytokine marker for primary graft failure after reperfusion (Fisher, et al., 2001). This foundational research exemplifies the potential role for systemic markers of inflammation in the predictive modeling of graft survival.

A recent study on lung donation after controlled cardiac death has demonstrated comparable early- and medium-term outcomes in contrast to donation after brain death (de Vleeschauwer, et al., 2011). These promising results introduce a potential for donor pool expansion in coordination with lung rehabilitation strategies prior to recipient lung implantation. A multicenter study has demonstrated a close relationship between graft ischemic time and both early gas exchange and long-term survival following single and double lung transplantation. The coordinated aim to increase the donor pool with donation after cardiac death and the principle strategy to minimize periods of warm and cold ischemia have inspired novel *ex-vivo* perfusion methods for the donor lung prior to recipient implantation (Cypel, et al., 2011a). An international commitment to technologic

advancement and scientific understanding promises to support improved outcomes and needed expansion of the donor pool for future generations.

The focus of this chapter is to define the principle immunologic and inflammatory mediators of IR injury, providing a mechanistic understanding for the multi-factorial pathogenesis of this clinical condition. Novel treatment strategies and current clinical methods for donor allograft treatment are reviewed as a foundational discussion for future research initiatives in the prevention of IR injury.

2. Cellular mediators of lung IR injury

A major complication after lung transplantation is IR injury. After the ischemic insult, reperfusion of the lungs is critical to maintain organ viability; however, reperfusion can also cause a wide variety of complex pathophysiological changes to the lung leading to inflammation and injury. IR causes a multi-faceted cascade of signal transduction events involving a milieu of pro-inflammatory cytokines and chemokines and the generation of reactive oxygen species (ROS) by a myriad of cells in the lung. The crosstalk between these cells via a plethora of molecules leads to the initiation and amplification of a signaling cascade that ultimately culminates in pulmonary injury and dysfunction. Many studies have now established that cells of the innate immune system (bone marrow-derived cells such as T cells, macrophages, dendritic cells and neutrophils) play an important role in lung IR injury. In addition, resident pulmonary cells, such as alveolar epithelial cells and endothelial cells, are also critical mediators of lung IR injury. These cell populations will be discussed below.

2.1 Neutrophils

One of the effector cells responsible for causing lung inflammation and injury are known to be neutrophils. Lung injury can be manifested by the multi-faceted role of infiltrating neutrophils to the site of injury, which adhere to and cross the endothelium upon activation. Although neutrophils play an important role in perpetuating lung IR injury, the role of neutrophils in the early phase is less predominant. Studies from Deeb and colleagues have shown that during the first few hours of IR injury, it is the neutrophil-independent events that play a major role and that neutrophil-dependent events exert their effects after several hours of reperfusion (Deeb, et al., 1990). Other studies have confirmed this biphasic cellular response and have suggested that T cells and macrophages have a more prominent role in the early phase of IR injury while neutrophils play a late, effector role in the execution of lung IR injury (Eppinger, et al., 1995; Fiser, et al., 2001). The infiltration and activation of neutrophils causes lung injury via release of oxygen free radicals and disruption of capillary-epithelial barrier which leads to increased microvascular permeability and pulmonary edema causing irreversible tissue damage.

2.2 Macrophages and dendritic cells

The role of antigen presenting cells such as macrophages and dendritic cells has been implicated in lung IR injury. Several studies suggest that lung IR injury is biphasic, with distinct acute macrophage-mediated injury followed later by neutrophil-dependent injury (Eppinger, et al., 1995, 1997; Fiser, et al., 2001a, 2001b). Abundant evidence suggests that alveolar macrophages in the donor lung are quickly activated by IR to subsequently release

pro-inflammatory chemokines and cytokines, and it has been demonstrated that depletion of alveolar macrophages attenuates lung IR injury (Naidu, et al., 2003; Zhao, et al., 2006). This acute pulmonary damage is followed by a cascade of events leading to activation of the recipient inflammatory system against the already damaged vascular endothelium and airway epithelium. A number of studies have strengthened a position for alveolar macrophages and TNF-α in acute IR injury (Eppinger, et al., 1997; Maxey, et al., 2004; Zhao, et al., 2006). One possible mechanism for decreased injury after suppression of macrophage function involves the attenuation of TNF-α or IFN-γ in respiratory burst activity and other inflammatory functions of macrophages (Arenzana-Seisdedos, et al., 1985; Eden & Turino, 1986; Issekutz & Issekutz, 1993; Mayer, et al., 1993; Phillips, et al., 1990). These studies indicate that IR injury is in part initiated by activated macrophages whereas delayed injury is mediated by activated neutrophils.

Recent studies have implicated a contributory role for dendritic cells in organ injury after transplantation including lung IR injury (He, et al., 2007; Saemann, et al., 2009). The cross-talk between antigen presenting cells like macrophages or dendritic cells and T lymphocytes has been postulated to play an important role in the initiation of lung IR injury. A detailed role for dendritic cells in lung IR injury, however, remains to be defined.

2.3 T lymphocytes

Involvement of T cells in IR injury until recently has not been considered; however, it has been demonstrated that T cells can be activated by antigen-independent mechanisms including oxygen radicals and cytokines such as TNF-α, IFN-γ, IL-23, IL-6, and RANTES (Bacon, et al., 1995). It is well known that the lung harbors a substantial reservoir of lymphocytes, and various subsets of T cells such as CD4+ T cells, CD8+ T cells, iNKT cells and γδT cells, have been implicated in lung IR injury. Yang *et al.* have recently demonstrated a key role for CD4+ T cells in an *in vivo* hilar clamp model of lung IR injury (Yang, et al., 2009). In the microcirculation, T cells may amplify inflammation by simultaneously binding to endothelial cells, macrophages, platelets and neutrophils. Several studies describe lung, renal and hepatic protection from IR injury in either null mice or T cell-depleted mice (Le Moine, et al., 2000; Rabb, et al., 2000; Sharma, et al., 2008; Zwacka, et al., 1997). These studies demonstrate significantly reduced neutrophil recruitment and inflammation in T cell-deficient mice after IR injury and suggest a role for T cells in the amplification of innate inflammatory signals. Clavien *et al*. described the activation of T cells by ROS during rat liver IR (Clavien, et al., 1993), and it appears that CD4+ T cells, but not CD8+ T cells, play a key role in the initiation of lung IR injury in mice (Sharma, et al., 2008). It has also been shown that acute lymphocyte-mediated lung IR injury involves CD40-CD40L signaling mechanisms (Moore, et al., 2002). CD4+ T cells play an important role in the initiation of immune responses by providing help to other cells and by taking on a variety of effector functions during immune reactions. CD4+ T cell priming results in the differentiation of various T cell subsets distinguished by the production of particular cytokines and effector functions.

Classically, CD4+ effector cells were viewed in the context of the Th1-Th2 cell paradigm, but other subsets have recently emerged including IL-17-producing T cells (Th17 cells), T cells with regulatory function (Treg cells) and invariant natural killer T (iNKT) cells (Larosa & Orange, 2008). There is also evidence that IL-23, IL-6, and TGF-β are proximal regulators of

IL-17 production by Th17 cells (Kolls & Linden, 2004) and iNKT cells (Rachitskaya, et al., 2008). iNKT cells are typically CD4+ T cells that share receptor structure with conventional T and NK cells and are characterized by their ability to rapidly produce immunoregulatory cytokines such as IL-4 and/or IFN-γ. NKT cells also constitutively express IL-23R and RORγt which can be rapidly activated during a variety of infections and inflammatory responses, and are recruited to produce IL-17 under emergency conditions. In the setting of renal IR, iNKT cell activation mediates neutrophil infiltration, IFN-γ production, and renal IR injury (Li, et al., 2007). Accumulating evidence suggest that Th17 cells are highly pro-inflammatory in that IL-17 is a key cytokine for the recruitment, activation and migration of neutrophils (Kolls & Linden, 2004), and Th17 cell-produced IL-17 is implicated in the pathogenesis of autoimmunity in various animal models (Bettelli, et al., 2007). However, the acute time frame of IL-17 production in lung IR injury is not consistent with a role for Th17 cells, which are not normally present in the lung and which require differentiation from naïve CD4+ T cells. Recent studies have revealed a critical role for the IL-23/IL-17 axis in various models of inflammation including IR injury (Edgerton, et al., 2008; Hanschen, et al., 2008; Wu, et al., 2007; Yen, et al., 2006). A critical role for iNKT cells and their rapid production of IL-17A in lung IR injury and neutrophil infiltration has been recently demonstrated using a mouse lung IR model (Sharma, et al., 2011). These studies support the concept that T lymphocytes can and do mediate IR injury.

2.4 Alveolar epithelial cells

The role of alveolar type II epithelial cells in lung IR injury has been described in recent studies (Sharma, et al., 2007). Alveolar type II epithelial cells contribute to lung IR injury via release of pro-inflammatory cytokines and chemokines. For example, it is well known that KC mediates lung injury by promoting infiltration of neutrophils. The crosstalk between macrophages and type II epithelial cells also contributes to the exacerbation of lung injury after IR. Sharma *et al*. showed that TNF-α production by alveolar macrophages mediates alveolar type II epithelial cell activation and KC production in an *in vitro* hypoxia-reoxygenation model (Sharma, et al., 2007). Recent studies also implicate alveolar type I cell-released mediators such as soluble receptor for advanced glycation end products (sRAGE) as a potential biomarker and indicator of lung injury after lung transplantation (Calfee, et al., 2007). This new marker may be useful given the recent discovery of the role of alveolar type I cells in alveolar fluid clearance (Johnson, et al., 2006). However, the exact role of alveolar type I cells in lung transplant biology remains less understood.

2.5 Endothelial cells

Increased endothelial permeability has been postulated to be the primary cause of IR-induced pulmonary edema (Hidalgo, et al., 1996). In a syngeneic rat lung transplantation model, it has been reported that the destruction of endothelial cell barrier promotes pulmonary edema and lymphocyte migration and that sphingosine 1-phosphate, a G protein coupled receptor agonist, reduces endothelial cell permeability and protects lung function and injury after IR (Okazaki, et al., 2007). Lung endothelial cells also mediate lung injury by contributing to oxidative stress (Balyasnikova, et al., 2005; Shuvaev & Muzykantov, 2011). Free radical production in endothelial cells via NADPH oxidase- or xanthine oxidase-dependent pathways results in elevated lung oxidant burden during

reperfusion (Al-Mehdi, et al., 1998). However, other cells such as leukocytes also contribute to free radical-mediated lung damage during IR injury (Shimoyama, et al., 2005). The prevention of the disruption of endothelial cell barrier is crucial for attenuation of lung injury after IR.

3. Reactive oxygen species (ROS) in lung IR injury

Lung IR injury is a complex pathological phenomenon encompassing various cellular, biochemical and molecular mechanisms. One of the key signaling pathways involving multiple cell types includes oxidative stress due to the generation of reactive oxygen species (ROS). Several groups have demonstrated that inhibition of enzymes involved in ROS generation can dramatically reduce the pro-inflammatory profile after IR.

3.1 ROS generation

A burst of ROS production occurs immediately upon reperfusion of hypoxic cells including leukocytes, epithelial cells and endothelial cells. The antioxidant defense capabilities of the lung are unable to cope with this ROS burst leading to altered cellular metabolic functions and redox signaling. Oxidative stress due to ROS generation causes pro-inflammatory cytokine release and enhanced transcription of numerous genes resulting in inflammation, cell injury, and neutrophil recruitment and activation in the lung after IR. Reperfusion of ischemic tissue results in generation of ROS such as superoxide ($\bullet O_2^-$), hydrogen peroxide (H_2O_2), and the hydroxyl radical ($\bullet OH$), which leads to oxidative damage to lung tissue (Al-Mehdi, et al., 1994; Al-Mehdi, et al., 1997; Ayene, et al., 1992; Eckenhoff, et al., 1992; Fisher, et al., 1991; Zhao, et al., 1997). This oxidative burst begins to directly increase the adherence of neutrophils to the endothelium (McIntyre, et al., 1995). The release of ROS not only induces cellular lipid membrane peroxidation and the production of inflammatory cytokines, but also plays a role in regulating the activity of several antioxidant enzymes (e.g. glutathione peroxidase, catalase and superoxide dismutase) as well as key transcription factors such as NF-κB and activator protein-1 (AP-1) (Cho, et al., 2006; Morimoto, 1993; Schreck, et al., 1992). Fisher *et al*. demonstrated oxygen-dependent lipid peroxidation during rat lung ischemia (Fisher, et al., 1991). Two key mechanisms of ROS generation in the lung include the NADPH oxidase system and activated xanthine oxidase, as discussed further below.

3.2 NADPH oxidase

Recent studies have demonstrated a key role of the NADPH-oxidase enzyme complex in ROS generation after IR (Goyal, et al., 2004; Jackson, et al., 2004; van der Vliet, 2008; Yang, et al., 2008; Yao, et al., 2007). NADPH oxidase, which is present in epithelial cells, endothelial cells, macrophages, T cells and neutrophils, among others, utilizes NADPH as a substrate to generate superoxide from molecular oxygen. Superoxide is usually rapidly converted to hydrogen peroxide (H_2O_2) or can react with nitric oxide ($NO\bullet$) to generate peroxynitrite ($ONOO^-$). Thus NADPH oxidase activity is a major source of ROS in the lung after IR. The upregulation of NADPH oxidase-generated ROS can contribute to IR injury through important redox signaling pathways such as the activation of MAP kinases, NF-κB and AP-1, which stimulates the production of proinflammatory cytokines. Pharmacological antagonism of NADPH oxidase by apocynin has been shown to protect against lung IR injury (Pearse & Dodd, 1999; Zhu, et al., 2008).

3.3 Xanthine and xanthine oxidase

Xanthine oxidase-dependent superoxide generation after IR is also a possible mechanism of lung injury (Kennedy, et al., 1989; Lynch, et al., 1988). Under ischemic conditions, xanthine dehydrogenase is converted to xanthine oxidase, which in turn converts hypoxanthine to xanthine and then further catalyzes the oxidation of xanthine to uric acid. In lung endothelium and alveolar type II epithelial cells, this conversion changes the normal degradation of hypoxanthine to uric acid into a source of oxygen radicals. The xanthine oxidase-generated free radicals damage endothelial cells as well as aid the sequestration of neutrophils thereby leading to further injury after IR. Treatment with xanthine oxidase inhibitors, such as allopurinol or iodoxamide, has been shown to attenuate superoxide generation and lung IR injury in rabbit and mouse models of lung IR injury (Adkins & Taylor, 1990; Kennedy, et al., 1989; Lynch, et al., 1988). These investigations suggest an important role for xanthine oxidase in the production of ROS during lung IR.

4. Cytokines and transcription factors

A multitude of experimental studies have shown that IR injury entails a rapid release of pro-inflammatory cytokines and chemokines. Additionally, measurable amounts of pro- and anti-inflammatory cytokines have been reported in lung tissue after lung transplantation in humans (de Perrot, et al., 2002). Important roles for TNF-α, IL-8 (KC in mice), IL-10 and IL-17 in the initiation and progression of lung IR injury have now been demonstrated. Gene modulation of transcription factors like NF-κB and AP-1 has also been correlated to the sequential events involved in lung IR injury.

4.1 Cytokines and chemokines

Cytokines and chemokines are immunomodulating protein molecules secreted by bone marrow derived cells as well as resident lung cells after IR injury. Pro-inflammatory cytokines and chemokines are known to play roles in IR injury of the heart, kidney, small bowel, skin, and liver; however, until recently less was known about their role in lung IR. The C-C family of cytokines and chemokines includes many putative mediators of macrophages, lymphocytes, and granulocyte-derived responses in IR injury (Oppenheim, et al., 1991; Strieter & Kunkel, 1993). This family includes MCP-1 (CCL2), MIP-1α (CCL3), MIP-1β (CCL4), RANTES (CCL5), MCP-3 (CCL7), MCP-2 (CCL8), as well as others. In addition to serving as chemotactic factors, C-C chemokines can modulate cytokine production, adhesion molecule expression, and mononuclear cell proliferation. Krishnadasan *et al*. demonstrated that TNF-α and IL-1β promote lung IR injury likely by altering the expression of other pro-inflammatory cytokines and by influencing neutrophil recruitment (Krishnadasan, et al., 2003). Antibodies to TNF-α, IFN-γ, and MCP-1 have been utilized to demonstrate the importance of these mediators in lung IR injury (Eppinger, et al., 1997). A prominent role for TNF-α was demonstrated both in the acute (30 min) and delayed (4 hr) phases of IR injury, while IFN-γ and MCP-1 appear to have roles only in the acute phase (Eppinger, et al., 1997). Not only is TNF-α produced by stimulated alveolar macrophages, it can also have significant effects on the macrophage respiratory burst, which may lead to oxidative tissue injury (Phillips, et al., 1990). In human lung transplantation, cytokines such as TNF-α, IFN-γ, IL-8, IL-10, IL-12 and IL-18 have been detected in lung tissue (de Perrot, et al., 2002). Mal *et al*. showed that early failure of lung transplants is

associated with massive release of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6 and IL-8 (Mal, et al., 1998).

Recent evidence has demonstrated a crucial role of IL-17 produced by iNKT cells in the initiation of lung IR injury via modulation of neutrophil infiltration and activation in an *in vivo* mouse model (Sharma, et al., 2011). On the other hand, a potent role for IL-10 as an anti-inflammatory molecule, promoting the abrogation of lung IR injury, has been shown in experimental lung IR models (Boehler, et al., 1998; de Perrot, et al., 2003; Fischer, et al., 2001; Martins, et al., 2004; McRae, et al., 2001). The cytotoxic and immunomodulatory effects of cytokines and chemokines are critical in the progression of lung IR injury. Taken together, the balance between pro- and anti-inflammatory cytokines is key to the outcome of lung injury after IR, and pharmacological modulation of these specific cytokine targets offers therapeutic potential for patients with primary graft dysfunction after lung transplantation.

4.2 Transcription factors

The activation of several aforementioned cytokines has been linked to the increased expression of key transcription factors like NF-κB and AP-1 after lung IR. A prominent role of gene regulation via these transcription factors in lung IR injury has been summarized by a number of previous studies.

4.2.1 NF-κB

In the cytoplasm, NF-κB is normally inhibited by IκB. Thus, a decrease in NF-κB activity, due to prevention of IκB degradation by pharmacological agents, leads to the attenuation of pro-inflammatory cytokine activation thereby leading to protection after lung IR. Inhibition of NF-κB via pharmacological agents like cyclosporine A or tacrolimus has been shown to offer protection from lung IR injury (Krishnadasan, et al., 2002). Treatment with pyrrolidine dithiocarbonate (another NF-κB inhibitor) has also been shown to improve lung function and attenuate lung IR injury in a porcine lung transplantation model (Ross, et al., 2000). Naidu *et al*. reported that simvastatin treatment attenuates lung IR injury via inhibition of NF-κB activity (Naidu, et al., 2003). Prevention of lung IR injury by pharmacological agents that inhibit NF-κB may offer a therapeutic strategy for patients with primary graft dysfunction after lung transplantation.

4.2.2 AP-1

The JNK/AP-1 pathway involves regulation of AP-1 by c-Jun kinase (JNK). Like NF-κB, AP-1 is also involved in the activation of several pro-inflammatory cytokines including TNF-α (Zhang, et al., 2002). For example, in a rat lung transplantation model, inhibition of AP-1 leads to decreased TNF-α expression in bronchoalveolar lavage fluid and a significant decrease in protein leakage resulting in decreased lung injury (Ishii, et al., 2004). Inhibition of the JNK/AP-1 pathway may also offer a potential therapeutic target to reduce lung IR injury.

5. Role of endogenous receptors in lung IR injury

Improving outcomes after lung transplantation and extending the donor pool and recipient criteria are predicated on the ability to minimize the deleterious inflammatory responses that occur with lung IR. Cellular receptor-mediated signaling is critical for the initiation and

modulation of inflammation and injury after IR. Using pharmacological agents that regulate receptor activation or antagonism, several ubiquitous cellular receptors like adenosine receptors, toll like receptors (TLRs) and receptor for advanced glycation end products (RAGE) have been shown to orchestrate lung IR injury.

5.1 Adenosine receptors

Adenosine is an endogenous mediator that generally serves as a cytoprotective modulator in response to various stress stimuli, and the protective effects of adenosine in the setting of organ IR injury have been shown in various studies (Day, et al., 2005, 2006; Reece, et al., 2008; Rork, et al., 2008). Adenosine signals through 4 subtypes of the G protein-coupled receptors, A_1R, $A_{2A}R$, $A_{2B}R$, and A_3R, all of which are expressed in the lung. Protective effects of adenosine receptor signaling classically occur through second messenger pathways such as the cAMP/PKA or phospholipase C pathways. Most studies have provided evidence that A_1R, $A_{2A}R$ and A_3R may primarily be involved in anti-inflammatory actions whereas the $A_{2B}R$ may have more pro-inflammatory actions in the lung (Anvari, et al., 2010; Ellman, et al., 2008; Gazoni, et al., 2010; Reece, et al., 2005, 2008; Rivo, et al., 2004; Sharma, et al., 2009, 2010; Sun, et al., 2006). However, the role of the $A_{2B}R$ in IR injury remains less understood. $A_{2A}R$ activation has shown remarkable attenuation of lung inflammation, decreased neutrophil infiltration, decreased vascular permeability and improved lung function in rabbit, rat and murine models of lung IR injury (Ellman, et al., 2008; Gazoni, et al., 2008; Lau, et al., 2009; Sharma, et al., 2009) as well as in a pig lung transplant model (Reece, et al., 2005). The anti-inflammatory effects of $A_{2A}R$ activation on CD4+ T cells has been shown to attenuate lung IR injury (Sharma, et al., 2010). In recent literature involving lung IR injury, pharmacological compounds modulating adenosine receptor agonism or antagonism have shown tremendous potential as possible therapeutic strategies for clinical applications to prevent or treat primary graft dysfunction after lung transplantation.

5.2 Toll-like receptors (TLRs)

TLRs are transmembrane receptors that play a crucial role in the innate immune response to a variety of trigger factors including IR injury (Marshak-Rothstein & Rifkin, 2007). TLR-2 and TLR-4 have been implicated in various models of IR injury (Arslan, et al., 2010; Leemans, et al., 2005; Oyama, et al., 2004). Lung biopsies of patients after lung transplantation showed elevated expression of mRNA for multiple TLRs (Andrade, et al., 2006), and lungs from TLR-4 knockout mice showed marked protection from lung IR injury (Shimamoto, et al., 2006; Zanotti, et al., 2009). Shimamoto *et al.* reported that TLR-4-mediated injury appears to occur through activation of c-Jun NH_2-terminal kinase (JNK) and translocation of NF-κβ.

5.3 Receptor for advanced glycation end products (RAGE)

RAGE is a multi-ligand receptor of the immunoglobulin superfamily expressed in most tissues and present on a wide range of cells where it plays a key role in inflammatory processes, especially at sites where its ligands accumulate. High-mobility group box 1 (HMGB1) is an intracellular protein, readily released from necrotic or damaged cells, that can signal through RAGE, TLR-2 or TLR-4, initiating an inflammatory response to further damage viable cells (Scaffidi, et al., 2002). Prior studies suggest that HMGB1 can interact

with both TLR-2 and TLR-4 to induce an inflammatory response during liver IR injury (Park, et al., 2006). Similarly, recent reports suggest a predominant role of RAGE and its ligand HMGB1 in the initiation of lung IR injury (Sternberg, et al., 2008). In a multi-center study, Christie *et al.* reported that an elevated plasma level of soluble RAGE (a truncated form of RAGE) was associated with primary graft dysfunction in patients undergoing lung transplantation (Christie, et al., 2009). An in depth characterization of the role of HMGB1, TLRs and RAGE remains to be elucidated in pulmonary injury after IR and transplantation.

5.4 Complement and fibrinolytic pathways

The complement system encompasses a collective term used for plasma and cell membrane proteins that play a role in cell defense processes. In lung IR injury, it has been shown that activation of the complement system leads to cellular injury through direct or indirect mechanisms (Bishop, et al., 1991; Naka, et al., 1997). In a swine single-lung transplantation model, the administration of soluble complement receptor 1, a potent inhibitor of complement activation, significantly reduces lung edema and improves lung function (Pierre, et al., 1998; Schmid, et al., 1998). In a clinical study, it was shown that complement inhibition by TP-10, a soluble complement receptor 1, significantly decreases the duration of mechanical ventilation in lung transplant recipients (Keshavjee, et al., 2005). This suggests that complement inhibition may offer additional therapeutic strategies for lung transplant patients. Further research is required to elucidate the specific pathways of the complement-mediated inflammation in lung IR pathophysiology.

The interplay between the fibrinolytic cascade and the inflammatory process in acute lung injury has been shown to be involved in lung IR injury. Tissue plasminogen activator (tPA), a member of the serine proteinase family, is expressed by vascular endothelial cells and functions to convert zymogen plasminogen to the active protease plasmin, thus initiating a potent fibrinolytic process. tPA knockout mice have attenuated lung inflammation by decreased neutrophil extravasation in a mouse model of lung IR (Zhao, et al., 2011). In the same study, it was shown that deletion of tPA leads to the concomitant downregulation of PECAM-1 expression via tPA/LRP/NF-κB signaling pathway and upregulation of P-selectin expression in small pulmonary vessels as well as to decreased MMP-9 expression. It has also been demonstrated that increased fibrinolysis through depletion of plasminogen activator inhibitor-1 (PAI-1), the endogenous tPA inhibitor, attenuated lung IR injury (Lau, et al., 2009). The complex molecular mechanisms involved in the fibrinolytic pathway and its potential role in clinical primary graft dysfunction remains to be further investigated.

6. Therapeutic strategies

Advancements in our understanding of molecular and pathophysiologic mechanisms for lung IR injury have supported significant research contributions aimed at improved allograft function. While no standardized treatment strategies specifically targeting IR injury exist, promising early results have demonstrated a potential role for *ex vivo* allograft treatment, nitric oxide therapy, and ischemic preconditioning in the prevention of IR injury.

6.1 Lung preservation strategies

A significant research commitment over the past decade has been invested in the creation of an ideal preservation and flush solution for lung transplantation. Intracellular solutions

with high potassium and low sodium are the current standard for kidney and liver transplantation, while extracellular solutions such as Perfadex® (Vitrolife, Gothenburg, Sweden) with low potassium, high sodium and dextran have emerged as the superior method for lung preservation (de Perrot, et al., 2003; Fischer, et al., 2001). Dextran induces erythrocyte deformation and prevents aggregation, preserving the pulmonary microcirculation and endothelial-epithelial barrier (Keshavjee, et al., 1992). This inherent quality may limit ischemia in regions of microcirculation thrombosis while creating an osmotic gradient that reduces protein and water extravasation during the reperfusion period (de Perrot, et al., 2003). In a clinical study, the absence of dextrose in extracellular solutions has been associated with an increased incidence of primary graft dysfunction and mortality (Marasco, et al., 2011; Oto, et al., 2006). While long-term outcomes remain the focus of future investigation, these findings support the clinical adoption of low-potassium dextran solutions as the primary method for lung allograft preservation.

6.2 Ex vivo lung perfusion (EVLP)

EVLP is an emerging technique for normothermic donor lung perfusion during the preservation period. EVLP with warm acellular Steen Solution™ (Vitrolife, Gothenburg, Sweden) following a period of cold storage is a promising modality for lung preservation with a demonstrated efficacy in the maintenance of lung function (Cypel, et al., 2008). This novel treatment strategy prevents ongoing injury and accelerates lung recovery (Cypel, et al., 2009). Recent prospective clinical data has demonstrated the successful transplantation of high-risk donor lungs following EVLP with comparable physiology to lungs transplanted under conventional methods of selection and transplantation (Cypel, et al., 2011b). These studies promote EVLP as a potential strategy for donor pool expansion and pre-implantation pulmonary function testing. In addition, this promising treatment strategy for lung rehabilitation may serve as a vehicle for future therapeutic treatment of the donor allograft during the inherent ischemic period.

6.3 Nitric oxide (NO)

NO is a messenger gas molecule with potent vasoregulatory and immunomodulatory properties (de Perrot, et al., 2003; Meyer, et al., 1998). NO inhibits xanthine oxidase as well as neutrophil chemotaxis and activation (de Perrot, et al., 2003; Meyer, et al., 1998). This mechanism of action establishes therapeutic potential for inhaled NO in the prevention of lung IR injury. NO ventilation during ischemia and following graft implantation in experimental models with *ex vivo* perfusion has demonstrated a reduction in pulmonary edema, improvement in oxygenation capacity, reduction in pulmonary vascular resistance, and decreased TNF-α with treatment (Dong, et al., 2009). Treatment of experimental recipient lungs with inhalational NO during reperfusion improved the ventilation-perfusion mismatch and decreased pulmonary artery pressures associated with IR injury (Adatia, et al., 1994). Unfortunately, this promising experimental data for inhalational NO has had limited translation to the clinical prevention of human lung IR injury. In a randomized clinical trial to evaluate the use of inhaled NO treatment, no significant differences in immediate oxygenation, time to extubation, length of intensive care unit stay or 30-day mortality were demonstrated (Meade, et al., 2001). While experimental data supports improved gas exchange with inhaled NO treatment, clinical lung transplantation data has

not yet demonstrated significant improvements in outcomes for lung transplantation recipients with inhaled NO treatment (de Perrot, et al., 2003) .

6.4 Preconditioning

Ischemic preconditioning enhances the ability of organs to withstand a sustained IR injury through repeated exposure to short periods of ischemia prior to the primary ischemic insult (Jun, et al., 2011). Ischemic preconditioning has demonstrated an ability to alter gene expression profiles within 6 hours of ischemia which is sustained until 24 hours following insult (Jun, et al., 2011). The proposed mechanism for ischemic preconditioning in the lung involves anti-inflammatory mediators, antioxidant stress, and the regulation of cellular energy metabolism (Jun, et al., 2011). Further experimental studies have suggested a role for adenosine A_1 receptor activation in the modulation of protective ischemic preconditioning (Yildiz, et al., 2007). Additional potential therapeutic preconditioning methods include hyperthermic and pharmacologic administration to improve the allograft response to the period of ischemia and subsequent reperfusion (Hiratsuka, et al., 1998; Schutte, et al., 2001). The role of preconditioning in clinical lung transplantation remains undefined (de Perrot, et al., 2003). Future application and study of preconditioning methods in the lung may demonstrate parallel beneficial effects to other organ systems, establishing this strategy for lung IR injury prevention.

7. Conclusions

Lung IR injury involves many cellular and molecular mechanisms making it a complex pathological process. Improvements in the technique of lung preservation and better understanding of the molecular mechanisms of IR injury are needed to prevent the occurrence of primary graft dysfunction after lung transplantation. The development of new strategies to improve the number of donor lungs available for transplantation could have a significant impact on the number of transplants performed and thus reduce the number of patients on the transplant waiting list. Additionally, improvements in lung preservation solution can help attenuate acute lung IR injury as well as chronic graft dysfunction. It is imperative that further experimental studies and multicenter clinical trials continue to be performed to reduce the morbidity and mortality associated with lung IR injury.

Research commitment to further define cellular responses to IR within the lung promises to support therapeutic advancement. Novel *ex vivo* treatment strategies may provide a therapeutic bridge for treatment of the donor allograft prior to recipient implantation. The combination of pharmacologic mechanistic inhibition and innovative approaches to sustained allograft perfusion support a promising future for lung transplantation. A dedicated and multidisciplinary approach to IR injury prevention is critical. Therapeutic advancement to ameliorate IR injury will increase the number of available donor grafts and improve lung transplantation outcomes for the increasing number of potential transplant recipients with end-stage pulmonary disease.

8. References

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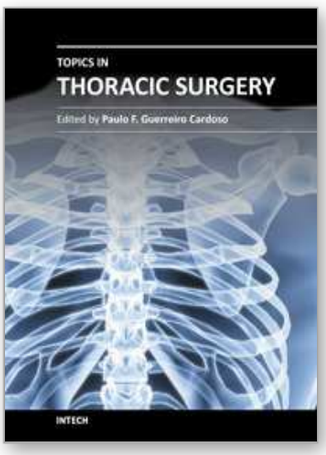
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